REMARKS

Claims 1, 3-12 remain in the application.

The present invention results from the discovery that by analyzing and correlating time-series data of biosignals with a change in MRI strengths, hard to examine parts of a brain of an examinee can be studied while reducing the burden on the examinee.

The present invention is a method and apparatus for analyzing brain functions which are capable of reducing the burden on an examinee as well as analyzing a function of a part of the brain which could not be easily analyzed. (Pg. 3) It accomplishes this by detecting biosignals, such as electroencephalograph, in parallel and separately from the examination conducted by an MRI system. (Pg. 3; Fig. 2) Parts of the brain that are functioning based on a correlation between the time-series data of the biosignals and change in the MRI strengths can then be analyzed. The examinee therefore does not have to perform any tasks and is only requested to sleep. (Pg. 3) This is particularly useful for examinees with a malady or disorder in her brain since the examination burden for the examinee is reduced. (Pg. 4) Furthermore, the present invention allows the study of specific parts of the brain that were previously hard to study such as the thalamus, putamen, and pons. The study of these parts of the brain is significant because these parts of the brains have been linked to memory processing. Thus, analyzing these parts of the brain can possibly lead to diagnoses to multiple devastating disorders such as disturbance of memory, Alzheimer's, Parkinson's disease, etc. (Pg. 5).

The Office Action rejected Claims 1, 3, 5-8, 11, and 12 under 35 U.S.C. §103(a) as being unpatentable over Kjaer, *Regional Cerebral Blood Flow During Light Sleep – a* H_2^{15} *O-PET Study* (hereinafter "*Kjaer*").

Kjaer is directed towards testing two hypotheses: (1) that regional cerebral blood flow ("rCBF") differed between the awake relaxed state and stage-1 sleep, and (2) that hypnagogic hallucinations frequently experienced at sleep onset would be accompanied by measurable changes in rCBF. Both hypotheses were tested using positron emission tomography ("PET") scans on. (Summary) First a patient was injected with 300-400 MBq $H_2{}^{15}O$ tracer using an automated injection system. Then patients were scanned for 90 seconds followed by a 10 minute break between scans. The first two scans were always performed before the subjects fell asleep. Immediately after each scan, the subject went through an interview starting with a short, loud wakeup-beep. (Pg. 202, ¶ 5). The EEG from the moment the tracer was injected until the start of the interview was evaluated in a blinded fashion by an EEG- sleep investigator. All EEG recordings with sleep spindles or K-complexes were discarded. (Pg. 202, ¶ 7) For all subjects isotope decay of the complete brain volume was sampled. (Pg. 202, ¶ 8) All intrasubject images were aligned on a voxel-by-voxel bases and the average PET scans were subsequently transformed into the standard stereotactic atlas of Talairach and Tournoux (1988) using the PET template defined by the Montreal Neurological Institute. Before statistical analysis, images were filtered with a 16-mm isotropic Gaussian filter to increase the signal-to-noise ratio. (Pg. 202, ¶ 9)

To test the first hypothesis, a group of stage-1 sleep scans were compared with the group of awake scans from subjects presenting both. To test the second hypothesis all scans in each of the two conditions of stage-1 sleep, i.e. with and without hypnagogic hallucinations were compared from subjects presenting both. (Pg. 202, ¶ 10).

Kjaer does not teach or suggest "a functioning part location calculating means for obtaining information on an MRI signal strength at each stage where the examinee is in a predetermined sleeping stages 1, 2, 3, 4, and REM and where the examinee is in a predetermined

waking stage." *Kjaer* only discloses receiving data from stage 1 sleep and the condition of awake relaxation. To test the first hypothesis, a group of stage-1 sleep scans were compared with the group of awake scans from subjects presenting both. To test the second hypothesis all scans in each of the two conditions of stage-1 sleep, i.e. with and without hypnagogic hallucinations were compared from subjects presenting both. (Pg. 202, ¶ 10) Furthermore, in *Kjaer*, all EEG recordings with sleep spindles or K-complexes are discarded. (Pg. 202, ¶ 7). A spindle, however, occurs in the second sleeping stage. (Pg. 12, lns. 21 – 23 of the present invention). Thus, *Kjaer* only teaches analyzing stage 1 sleep in comparison with awake relaxation and does not teach analyzing the sleeping stages 1, 2, 3, 4 and REM.

In contrast, the present invention analyzes REM and all four stages of sleep including sleeping stage 1 (hypnagogic period and initial light sleeping period), sleeping stage 2 (light sleeping period), sleeping stage 3(medium-level sleeping period), and sleeping stage 4 (deep sleeping period) by comparing it to periods of non-activity such as in the waking stage. (Pg. 10, ln. 13 – Pg. 11, ln. 3). Furthermore, as noted in specification of the present invention, sleeping stage 2 allows a spindle having a frequency in the vicinity of 12 to 14 Hz and a K-complex to appear. (Pg. 10, ln. 24 – Pg. 11, ln. 2). By determining activity within the brain, parts of the brain such as the thalamus, pons, putamen in basal ganglia which may have a close relation to memory processing and which are difficult to analyze in a waking stage can be analyzed by the present invention. (Pg. 13, ln. 17 – Pg. 14, ln. 1). Furthermore, since the examinee is sleeping, the patient does not need to be disturbed, which would be particularly useful for patients with a malady or disorder. (Pg. 14, lns. 2 – 10).

Kjaer also does not disclose "examination of the brain of the examinee in a state without external stimuli conducted by an MRI System." In *Kjaer*, "Immediately after each scan, the

subject went through an interview starting with a short, loud wakeup-beep." The subjects then reported whether they felt they were awake or asleep at the time of the beep, and on a scale from 0 to 5 assessed the visual and auditory power of their thoughts including how realistic and how leaping the thoughts were. (Pg. 202, ¶ 6). Thus, *Kjaer* provides external stimuli to the patients.

In contrast, the present invention, analyzes the patient's brain "in a state without external stimuli." Thus, the present invention does not impose any task on the patient from the outside. (Spec., Pg. 4). The present invention seeks to reduce the examination burden on the patient, which is why, for example, the patient is only asked to sleep rather than fulfill a certain task such as "watching a picture, listening to a sound, doing a finger exercise, [or] answering a question on words. . . ." (Pg. 3, lns. 17-19). This can be helpful in analyzing the brains of patients who have a malady or disorder in their brains.

Furthermore, as the Office Action notes, *Kjaer* uses a PET scan instead of an MRI. However, the Office Action cites to *Langleben* (U.S. Patent App. No. 2005/0154290) for the proposition that it would have been obvious to use an MRI system instead of a PET scan. However, there is no indication in *Langleben* that it is suitable for analysis without external stimulus or analysis in conjunction with biosignals.

Langleben is a method and system for measuring changes in the brain activity to determine whether an individual is being truthful or deceptive, and/or whether an individual has prior knowledge of a certain face or object. (Abstract).

However, *Langleben* only teaches using an MRI system for detection of brain activity where there is an external stimulus. *Langleben* is used with the Guilty Knowledge Test ("GKT"), a method of polygraph interrogation that facilities psycho-physiological detection of prior knowledge of crime details that would be known only to a suspect involved in the crime.

In a typical laboratory GKT, the subject is instructed answer "No" in response to a series of questions or statements, the answer to some of which is known to be "Yes" to both the investigator and the participant; however the participant may be unaware of the investigator's knowledge. (¶¶ 0018; 0028; 0033) Thus, *Langleben* only discloses that an fMRI analysis is appropriate when the suspect is subjected to an external stimulus and there is no indication that it is appropriate when the subject is not subject to any external stimulus.

In contrast, the present invention performs an "examination of the brain of the examinee in a state <u>without external stimuli</u> conducted by an MRI System." (emphasis added) Again, the present invention does not impose any task on the patient from the outside to reduce the examination burden on the patient. (Pg. 3, lns. 17-19). This can be helpful in analyzing the brains of patients who have a malady or disorder in their brains.

Furthermore, *Langleben* also does not teach that an MRI system would work in conjunction with systems which uses biosignals such as EEG signals. *Langleben* only discloses that using an fMRI is advantageous over using an EEG system when detecting brain activity because the fMRI can localize the source of changed signals with a spatial resolution in the order of 3mm, while the source of the signal in EEG cannot be establish with such certainty. (¶ 0009). Therefore, there is no indication in *Langleban* that fMRIs can be used with EEG analysis.

Thus, *Langleben* does not teach that it would have been obvious to one skilled in the art to use an MRI system instead of a PET scan.

Furthermore, PET scans are different from MRI scans. PET scans require an injection of nuclide-labeled tracer such as MBq H_2^{15} O into the patient. (Pg. 202, ¶ 5) Therefore, the PET scan is invasive and can be painful for a person with a debilitating disease. In addition the injection of a nuclide-labeled tracer means that the patient is exposed to nuclear radiation made

by positron decay. Therefore, unlike MRIs, the patient is under constant exposure to nuclear material during a PET scan. Furthermore, due to this exposure, PET scans may be limited in the amount of scans it can perform per night.

In contrast, the present invention is designed to aid analysis of brain functions of people with maladies or disorders. Thus, it seeks to minimize the burden on the individual. In addition, the present invention indicates the inferiority of PET scans for its purpose stating that "since such a PET system has a very low time resolution as compared to the MRI system, it is difficult for the PET system to analyze brain functions related to memory processing for each of minutely divided sleeping stages." (Pg. 2, lns. 18-22). The present invention can complete a scanning cycle 500 times in about 67 minutes. (Pg. 8, lns. 11 – 13).

Therefore, it would not be obvious to use an MRI system instead of a PET scan.

All arguments for patentability with respect to Claim 1 are repeated and incorporated herein for Claims 5 and 6.

The Office Action rejected Claim 4 under 35 U.S.C. §103(a) as being unpatentable over *Ives* (U.S. 5,445,162).

With respect to Claim 4, the Office Action admits that *Kjaer* does not teach or suggest wherein "the detection of the biosignal of the examinee by the biosignal detection means and the examination of the brain of the examinee by the MRI system are performed alternately."

However, *Ives* also does not teach or suggest wherein "the detection of the biosignal of the examinee by the biosignal detection means and the examination of the brain of the examinee by the MRI system are performed alternately."

Ives is directed towards an invention which records EEG activity simultaneously with MRI scanning. (Abstract) It accomplishes this by reduing the amount of magnetic metal and

raio frequency generating equipment associated with the recording of the EEG that is within the bore of the MRI magnet, and moving all significant radio frequency generating equipment outside the MRI room. (Pg. 1, lns. 60 – 65).

Ives does not teach alternating recording EEG and MRI signals, but rather teaches performing numerous activities and manipulations of the MRI machine to allow the EEG and the MRI to be recorded simultaneously. This can be expensive since it may require huge modifications of existing facilities.

In contrast, in the present invention a scanning cycle of about 8 seconds comprises a scanning period by the MRI of about 4 seconds and a scanning halted period of about 4 seconds following the scanning period. (PG. 8, lns. 2 – 13). During the scanning halted period, the biosignal detection means 1 utilizes the EEG signal detected signal for its analysis. (Pg. 9, lns. 6- 5).

Claims 1 and 3-12 depend from and further define Claims 1 and 6 and are thus patentable, too.

If the Examiner believes that a telephone interview will help further the prosecution of this case, he can contact the undersigned attorney at the listed telephone number.

Very truly yours,

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